

Case Report

Alymphoid cystic thymic dysgenesis - FOXN1 gene mutation: a rare case report of two siblings

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ABSTRACT

Alymphoid cystic thymic dysgenesis is a severe combined immunodeficiency (SCID) syndrome caused by a mutation in fork head box N1 gene (FOXN1) on chromosome 17. It is a transcriptional factor regulating the development, differentiation and function of thymic epithelial cells; maintaining T-lineage progenitors in bone marrow; promoting terminal differentiation of epithelial cells of hair follicles. Mutation in FOXN1 is known to cause a rare disorder characterized by rudimentary thymus gland (primary lymphoid organ for T-cell differentiation), T-cell immunodeficiency, congenital alopecia totalis and nail dystrophy. Here we report two affected siblings from a non-consanguineous family with similar features of alopecia totalis, nail dystrophy and failure to thrive. The first child was a 7-month-old female baby, with history of two hospitalization in the past for lower respiratory tract infection, had left axillary lymphadenopathy (BCG adenitis), alopecia totalis, nail dystrophy and hepatosplenomegaly. Bronchoalveolar lavage secretion was positive for *Mycobacterium tuberculosis* and *Pneumocystis carinii* pneumonia by gene Xpert and polymerase chain reaction respectively. Immunodeficiency panel workup revealed combined T cell and B cell immunodeficiency, genetic analysis by whole exome sequencing revealed recessive missense mutation in exon 6 of FOXN1 gene on chromosome 17. Due to lack of sufficient literature it was reported as variant of unknown significance and to establish its clinical significance the carrier status of both the parents was established. Second child presented to us at 3 months of age, also had similar phenotypic features and on evaluation had very low lymphocyte subset count however mutational analysis could not be done in this child due to parent's denial. Hence, we conclude this child also was affected.

Keywords: Alymphoid cystic thymic dysgenesis, SCID, FOXN1, Alopecia, Nail dystrophy

INTRODUCTION

Fork head box N1 (FOXN1) gene mutation or alymphoid cystic thymic dysgenesis (ACTD) is a rare autosomal recessive primary immunodeficiency disorder, characterized by a triad of T-cell immunodeficiency, congenital alopecia and nail dystrophy (TIDAND). It is disorder of both cell-mediated and humoral immunity characterised by high susceptibility to develop severe and sometimes fatal infections. This disorder is the human

counterpart of the nude/SCID in mouse. The phenotype due to mutation of the transcription factor FOXN1 was first described in mice by Flanagan in 1966, who noted an absence of hair, poor growth, early mortality, and susceptibility to infection.¹ The molecular cause was identified in 1994 to be due to mutation in the *whn* gene, later renamed FOXN1.² In 1996 two sisters from Italy were the first to be reported with the features of FOXN1 gene mutation.³

CASE REPORT

A 7-month-old female baby, first child of a non-consanguineous married couple having uneventful neonatal period with past history of recurrent lower respiratory tract infection (LRTI) requiring admissions was brought with severe pneumonia. On examination child was alert, tachypneic, had alopecia totalis, nail dystrophy, Bacillus Calmette-Guerin (BCG) adenitis (Figure 1), and hepatosplenomegaly. Hence a provisional diagnosis of disseminated BCG with primary immunodeficiency was considered & worked up. Bronchoalveolar lavage secretion was positive for Mycobacterium tuberculosis and Pneumocystis carinii pneumonia by gene X-pert and polymerase chain reaction (PCR) respectively. Immunoglobulin levels normal (Table 1). Computed tomography (CT) thorax showed right upper lobe and perihilar consolidation with absent thymus gland (Figure 2). Child was treated with antibiotics, Antitubercular therapy and trimethoprim/sulfamethoxazole.



Figure 1: First child – (A) alopecia totalis, (B) BCG adenitis, and (C) dystrophic nails.

Table 1: Immunoglobulin levels of first child.

Immunoglobulin type	Observed value (mg/dl)	Reference interval (mg/dl)	Inference
IgG	318	350-1620	Normal
IgA	26.5	1-91	
IgM	41.7	6-66	
IgE	3.93 IU/ml	Up to 15 IU/ml	

Immunodeficiency panel workup revealed combined T cell and B cell immunodeficiency, hence fluconazole and valganciclovir prophylaxis was started. Genetic analysis was carried out by whole exome sequencing (Sanger sequencing), which detected a homozygous missense mutation in exon 6 of FOXN1 gene on chromosome 17 (G959A/Arg320Gln) (Figure 3). Due to lack of sufficient literature it was reported as variant of unknown significance and to establish its clinical significance, carrier testing of parents was done which revealed

heterozygous mutation of the same gene in both the parents.



Figure 2: CT chest of first child.

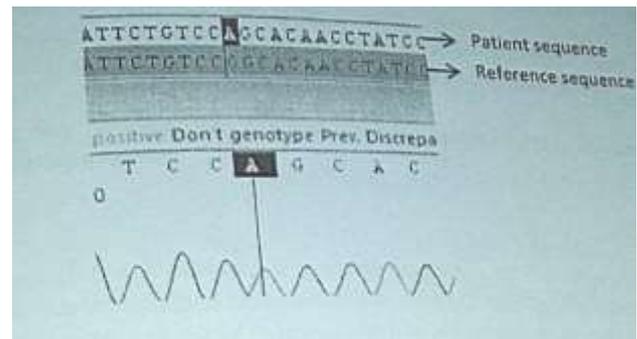


Figure 3: Whole exome sequencing report of first child.



Figure 4: Second child- (A) alopecia totalis, and (B) dystrophic nails.

This child succumbed at 9 months of age. Despite genetic counseling, parents had a second male child who also had similar phenotypic features - alopecia totalis and dystrophic nails (Figure 4) and was admitted at 3 months of age with respiratory failure. Immunoglobulin analysis showed low levels of immunoglobulin G (Table 2). Flow

cytometric analysis of lymphocyte subsets was performed which revealed very low levels of all the lymphocyte subsets (Table 3). However, it could not be genetically confirmed due to parents' denial. This child succumbed

due to severe respiratory infection at 4 months of age. In view of similar course of events as that of his elder sibling, it was concluded that the same syndrome was affecting this sibling also.

Table 2: Immunoglobulin levels of second child.

Immunoglobulin type	Observed value (mg/dl)	Reference interval (mg/dl)	Inference
IgG	168	350-1620	Decreased
IgA	6.5	1-91	Normal
IgM	38.5	6-66	
IgE	3.0 IU/ml	Up to 15 IU/ml	

Table 3: CD3/CD4/CD8/CD45 cell counts of second child.

Test description	Observed value	Unit	Biological reference interval
CD 45 absolute (lymphocyte gated)	2054	/c.mm	1000-3000
CD 3 (T Cells) percentage	4.65	%	53-84
CD 3 (T Cells) absolute	96	cells/ μ l	2500-5500
CD 4 (helper T Cells) percentage	Below 4	%	35-64
CD 4 (helper T Cells) absolute	63	cells/ μ l	1600-4000
CD 8 (suppressor T-Cells) Percentage	Below 4	%	12-28
CD 8 (suppressor T-Cells) Absolute	35.00	cells/ μ l	560-1700
CD 4/CD 8 ratio	-		\geq 1.0

DISCUSSION

SCID is very rare disorder with an estimated incidence of $<1/1,000,000$.⁴ Amongst this group a lymphoid cystic thymic dysgenesis (ACTD) is even rarer disorder, only nine cases have been reported in the literature to date. It is inherited in an autosomal recessive pattern caused by a biallelic missense mutation in FOXP1 gene. The FOXP1 is a transcriptional factor regulating the development, differentiation and function of thymic epithelial cells; maintaining T-lineage progenitors in bone marrow and promoting terminal differentiation of epithelial cells of hair follicles.

The first human cases of FOXP1 deficiency were reported by Pignata et al in 2 children in the Italian community in 1996 with athymia (resulting in T-cell deficiency), absence of hair, and nail dystrophy.³ In the same community, 4 other children with alopecia had died early in life from severe infections, which suggested that they, too, had the same FOXP1 mutation. In 2004, a screening search for this FOXP1 mutation was undertaken in the community where the probands originated as part of a program to provide genetic counselling and prenatal diagnosis support. This program led to the identification of 55 subjects who carried the heterozygous FOXP1 mutation, all belonging to the same extended pedigree as the 2 siblings described by Pignata et al.^{2,5} In 2017 Ramadevi et al reported the first case in a one month old female baby from India.⁶

Most of the affected individuals live only up to infancy or early childhood. Disease manifestation usually occurs in infants or sometimes in the fetus. Infants manifest with

clinical hallmarks of alopecia totalis, nail dystrophy, recurrent diarrhea, oral candidiasis, failure to thrive, erythroderma, lymphadenopathy and repeated severe persistent infections starting early in life. The infections result in failure to thrive and can even be life threatening. Amorisi et al have described a human aborted fetus homozygous for a mutation in FOXP1 gene who lacked the thymus and also had abnormal skin, anencephaly and spina bifida, they found that FOXP1 gene is expressed in mouse developing choroid plexus.^{7,8} These observations suggest that FOXP1 may be involved in neurulation in humans but it is still unclear whether central nervous system abnormalities are a common feature of this disorder. Heterozygous carriers manifest koilonychia, Beau line, and leukonychia, characterized by a typical arciform pattern resembling half-moon and involving the proximal part of the nail plate.

The first described human FOXP1 mutation was a C792T transition in exon 5 resulting in the nonsense mutation R255X, and was detected in two probands originated from a small community in southern Italy. The same mutation was observed in the case reported by Ramadevi et al.⁶ Probably, it is attributed to migration of people from the Italian peninsula to India mainly as merchants since Roman times.

The whole exome sequencing in our case identified three missense variant's FOXP1 (homozygous), SLC4A1 (heterozygous), EVC2 (heterozygous). The FOXP1 gene (Chr 17:26861380, c. G959A, p. Arg320Gln) a homozygous 'pathogenic' disease-causing variant was detected in exon 6. As per the pathological transcript (Ref Seq ID: NM_003593), this variant is in exon 6. Two other

heterozygous variants of unknown significance' (VUS) were detected in exon 5 of the SLC4A1 gene (Chr17:42338179, c. A173G, p. Tyr58Cys) and in exon 14 of the EVC2 gene (chr4:5624455, c. G2310T, p. Trp770Cys). The identified homozygous missense substitution (c. G959A/p. Arg320Gln) in FOXN1 gene is predicted to cause loss of function. The resultant protein is likely to lack the DNA binding and transactivation domains; thus, will likely to result in loss-of function.

Patients with FOXN1 mutation may not respond well to hematopoietic stem cell transplantation, as it is not curative, unrelated allogeneic thymic transplantation offers a potential cure.⁹ The thymic tissue routinely discarded during cardiac surgeries of infants is used for transplantation. Markert et al reported two cases of thymus transplantation in two FOXN1-deficient subjects, after transplantation naive T cells and diverse TCR repertoires developed in parallel with normalization of T-cell proliferative responses and immunoglobulin levels.¹⁰ More importantly, the associated clearance of the ongoing disseminated infections raises the expectation that this therapeutic approach may have long-term clinical benefit for subjects with athymia secondary to FOXN1 deficiency. Overall, thymus transplantation offers a promising treatment for FOXN1 deficiency (nude/SCID).

CONCLUSION

Recurrent LRTI in a child with ectodermal changes should raise suspicion of SCID in particular FOXN1 gene mutation. It is advisable to perform exome sequencing of such children and their parents so that appropriate prenatal genetic counselling can be done.

As no curative treatment is available for this condition till date, further research is required in terms of treatment of this condition.

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